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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,317	04/17/2000	ERNST WAGNER	0652.2070000	2149

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05/06/2002

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 05/06/2002

20

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/446,317

Applicant(s)

WAGNER ET AL.

Examiner

Richard Schnizer

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-52 and 54-68 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 35-52 and 54-68 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

BEST AVAILABLE COPY**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1632

DETAILED ACTION

An amendment was received and entered as Paper No. 19 on 2/27/02. Claims 35-52 and 54-68 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The rejections of claims 35-45, 49, 52, and 65 under 35 USC 102 are withdrawn in view of Applicant's amendments.

The rejections of claims 35, 42, 44-52, and 54-68 under 35 USC 103 are withdrawn in view of Applicant's amendments.

Specification

The amendment filed 2/27/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "random branched" at page 6, lines 1 and 4. The specification as filed gave non-limiting examples of PEI which was suitable for the invention. The specification did not explicitly exclude any form of PEI from use in the invention. For this reason, the incorporation of the sub genus of "random branched" PEI constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office action.

Art Unit: 1632

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-52 and 54-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35-52 and 54-68 are amended to be drawn to compositions and processes involving “random branched polyethyleneimine (PEI)”. The specification as filed gave **non-limiting** examples of PEI which was suitable for the invention. See page 6 lines 1-10. However the specification did not explicitly exclude any form of PEI from use in the invention. For this reason, limitation of the claimed material to the sub-genus of “random branched” PEI constitutes new matter.

Applicant asserts at page 3 of the response that the introduction of the term “random branched” does not constitute new matter because it is a description of an identifying physical characteristic of the PEI products listed in the specification. Applicant states that “identification of a trademark by scientific or other explanatory language may be introduced by an amendment, **if restricted to the characteristics of the product known at the time the application was filed** to avoid any question of new matter.” Emphasis added. However in this case, the product in

Art Unit: 1632

question is “commercially obtainable PEI” (see page 6, line 1), and the specification as filed in no way **restricted** the characteristics of the commercially obtainable PEI usable in the invention to “random branched” PEI, or to those forms of PEI listed at page 6, lines 1-10. Applicant relies on the court’s decision in *Kennecott Corp. v. Kyocera Int’l Inc.* 5 USPQ 2d 1194 (Fed. Cir. 1987) to support the notion that inherent physical properties of a compound may be amended into the specification after the filing date without adding new matter. This is unpersuasive because the instant situations are not analogous. The specification as filed did not exclude any form of PEI from use in the invention. In the instant case, Applicant wishes to change the scope of the originally claimed invention. Whereas the specification as filed did not limit the nature of the PEI used in the invention to “random branched PEI”, this is precisely what Applicant wishes to do now. Because the specification as filed did not contemplate the exclusion of any form of PEI from the claimed subject matter, the limitation of the claims to the newly added sub-genus of “random branched PEI” constitutes new matter. The findings of the court in *Kennecott Corp. v. Kyocera* are not germane to this issue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1632

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 35-41, 46-52, 54, 55, and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US Patent 6,077,663) in view of Boussif et al (Proc. Nat. Acad. Sci. (1995) 92: 7297-7301)1995).

Curiel teaches compositions comprising polycations complexed with nucleic acids, wherein the polycation is conjugated to an internalizing factor. See abstract; column 25, lines 20-26; column 29, lines 17-24 and claim 1, column 91. The polycation may be PEI. See column 25, lines 20-26. The internalizing factor may be a hydrophilic polymer such as transferrin or EGF. See column 24, lines 7, 8, and 26. Curiel teaches that conjugation may be by covalent means. See column 34, line 28 to column 35, line 21. Curiel also teaches other means of covalently coupling molecules to polycations, such as the use of bifunctional cross-linking reagents. See column 17, line 60 to column 18, line 33. The charge ratio of DNA to PEI should be approximately 1:1, thus the ratio of DNA phosphates to PEI nitrogens should be about 1:1. See column 25, lines 32 and 33. The molar ratio of hydrophilic internalizing factor to polycation may be about 1:3. See e.g. paragraph bridging columns 34 and 35, especially column 35, lines 6 and 7. The nucleic acid may encode a cytokine or a tumor antigen. See e.g. column 25, lines 59-64; and column 33, lines 32-36. In one example, the concentration of DNA in a transfection composition was 6 micrograms per 0.17 ml. See sentence bridging columns 40 and 41.

Curiel is silent as to the structure of the PEI, specifically with regard to the nature of any branching, so Curiel does not explicitly teach random branched PEI. Curiel is silent as to the

Art Unit: 1632

molecular weight of the PEI, although Curiel teaches that the molecular weight of the polycation is not critical as long as it is sufficient to provide electroneutrality when complexed with nucleic acid. See column 25, lines 32-44. Curiel does not teach a transfection composition comprising DNA at a concentration of 200 micrograms/ml to 1 microgram/ml.

Boussif teaches the use of PEI to form transfection complexes with DNA. See abstract. The PEI was either 50 kDa or 800 kDa. See page 7297, column 2, lines 1 and 2 of second full paragraph. PEI 800 kDa was obtained from Fluka. PEI 50 kDa was obtained from Sigma. The instant specification teaches that these preparations are random branched PEIs. See page 6, lines 1-3. Boussif also teaches an optimal ratio of PEI nitrogen to DNA phosphate in the range of 9-13.5. See e.g. Fig. 2 on page 7299.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the random branched PEI of Boussif in the invention of Curiel. One would have been motivated to do so given the suggestion of Curiel to use PEI, and the teaching of Boussif that PEI gave better transfection results than lipopolyamines (see abstract of Boussif). Because Curiel is silent as to commercial providers of PEI, one would have looked to the available art for guidance in this regard. Boussif teaches that 800 kDa PEI from Fluka provides particularly efficient transfection. See page 7299, column 2, first sentence of first full paragraph, and Fig. 4.

Although Curiel does not explicitly teach a composition comprising DNA at a concentration of 200 micrograms/ml to 1 microgram/ml, as required by claim 66, differences in concentration will not generally support the patentability of subject matter encompassed by the

Art Unit: 1632

prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case, there is no such evidence of record. Furthermore, and the specific concentration of DNA in a transfection complex is recognized by those of ordinary skill in the art to be a result-effective variable which is routinely optimized.

Claims 35-41, 46-52, 54, 55, and 64-68 are product by process claims in which the processes by which the product may be made are not considered to materially affect the claimed product. Because the combination of Curiel and Boussif renders the product obvious, the invention as a whole was *prima facie* obvious.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel and Boussif as applied to claims 35-41, 46-52, 54, 55, and 64-68 above, and further in view of Ezzidine et al (New Biol. (1991) 3(6): 608-614).

Curiel and Boussif can be combined to render obvious a composition comprising a nucleic acid and random branched PEI, wherein the random branched PEI is covalently bound to a hydrophilic polymer.

Ezzidine teaches a method of transfecting cells *in vivo* using retroviral vectors comprising a nucleic acid encoding herpes simplex thymidine kinase. See abstract.

It would have been obvious to one of ordinary skill in the art to substitute the PEI/DNA transfection complexes of Curiel and Boussif for the retroviruses of Ezzidine. One would have been motivated to do in order to avoid the safety risks of retroviral vectors, as taught by Curiel.

Art Unit: 1632

Use of the composition of Curiel and Boussif would also allow the inclusion of other genes such as those encoding detectable markers, whereas retroviruses would be less advantageous for this purpose in view of restrictions on the amount of genetic material one can incorporate. See Curiel, column 2, lines 51-61.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments have been fully considered, but they do not apply to the new grounds of rejection set forth above.

Conclusion

No claim is allowed. Claims 42-45 and 58-63 are free of the art of record.

Applicant's amendments necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

Art Unit: 1632


CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



JAMES KETTER
PRIMARY EXAMINER